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EFFECTS OF SCHEDULE OF REINFORCEMENT ON A PENTOBARBITAL DISCRIMINATION IN RATS

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The purpose of this study was to determine the effects of the schedule of reinforcement on a pentobarbital discrimination in rats. Five rats were trained to discriminate 10 mg/kg pentobarbital from saline under a multiple fixed-interval 180-s fixed-ratio 20 schedule of reinforcement. During both saline and pentobarbital training sessions, subjects emitted a higher percentage of correct responses under the fixed-ratio component as compared to the fixed-interval component of the multiple schedule. Determination of the pentobarbital dose–response curve under the fixed-ratio component resulted in a steep curve characterized by responding on the saline lever at low doses and on the drug lever at higher doses. Under the fixed-interval component, a graded dose–effect curve was produced, with considerable responding on both levers after intermediate doses of pentobarbital. The administration of phencyclidine and MK-801 resulted in an intermediate level of drug-lever responding for some subjects. Administration of *d*-amphetamine resulted in saline (nondrug) appropriate responding. The results of this study demonstrate that the schedule of reinforcement is a determinant of drug stimulus control, just as it is a determinant of other drug effects.

Key words: drug discrimination, multiple schedule, pentobarbital, phencyclidine, MK-801, *d*-amphetamine, lever press, rats

In drug-discrimination studies, a subject is trained to emit one response when the stimulus effects of the drug are present and to emit a different response when the drug stimuli are absent (Overton, 1984). A reinforcer is delivered only after the subject completes the schedule requirements appropriately. Typically, the number of responses emitted on the drug-appropriate alternative divided by the total number of responses is considered to be a measure of stimulus control in the individual animal.

Through its control of responding, the schedule of reinforcement plays a primary role in the formation of stimulus control. For example, Koek and Slangen (1982) and McMillan and Wenger (1984) established drug discrimination with asymmetrical reinforcement densities for drug and vehicle responding. That is, the subjects could earn more reinforcers for correct responding under one stimulus condition than under the alternative stimulus condition. This reinforcement asymmetry produced biased responding toward the stimulus associated with the greater reinforcement density. These studies have shown that the schedule of reinforcement is an important determinant of stimulus control by drugs.

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Among the schedules used in drug-discrimination studies, the fixed-ratio (FR) schedule has been used most frequently (Colpaert, 1987). Other reinforcement schedules that have been used include fixed-interval (FI) schedules (Krimmer, McGuire, & Barry, 1984; Kubena & Barry, 1969), variable-interval (VI) schedules (Gouvier, Akins, & Trapold, 1984), tandem VI FR schedules (Witkin, Carter, & Dykstra, 1980), and second-order FR (FR) color-tracking schedules (McMillan, Cole-Fullenwider, Hardwick, & Wenger, 1982). Although a variety of schedules have been used to investigate the stimulus effects of drugs, the manner in which different reinforcement contingencies produce differential effects on drug-discrimination behavior has not been explored systematically.

The purpose of this study was to determine how the schedule of reinforcement influences drug discrimination. To assess this influence, fixed-ratio (FR) and fixed-interval (FI) schedules were presented to the subjects as components of a multiple schedule (mult FR FI). Pentobarbital was chosen as the training drug because of the relatively rapid establishment of stimulus control with this drug (Overton, 1984). Phencyclidine (PCP) and MK-801 were studied under the multiple schedule because of the partial generalization of these drug stimuli to that of pentobarbital (Willetts & Balster, 1989). To assess the specificity of the stimulus control of behavior under the mul-

tiple schedule components, *d*-amphetamine was also studied.

METHOD

Subjects

Five adult (approximately 90 days old) male Sprague Dawley rats, obtained from Charles River, served as subjects. They were housed individually in a large colony room with continuous access to water. A light–dark cycle of lights on at 7:00 a.m. and lights off at 7:00 p.m. was in effect in the colony room for the entire study.

Apparatus

Sessions were conducted using a standard Gerbrands two-lever operant chamber (Model G7322). The two levers were located 8.5 cm above the floor of the chamber on either side of a rectangular opening 2 cm above the floor that served as a receptacle for the delivery of 97 mg (Noyes Formula A) food pellets. A bank of four lights (28-V DC lights with translucent blue covers) was mounted above each lever. Two 28-V DC houselights in the back quarter of the top Plexiglas panel provided general illumination. The operant chamber was placed in a sound-attenuating enclosure equipped with a fan for ventilation and a speaker that generated white masking noise. The control of the behavioral contingencies and data collection were accomplished with a TRS-80® model III microcomputer (Radio Shack) interfaced with a Microcomputer Interface II® (Med Associates, Inc.). The microcomputer and interface were located in a room adjacent to that of the operant chamber.

Procedure

The rats were given free access to food in the home cage and were weighed for 7 consecutive days to assess their free-feeding weights. The subjects were then placed on a restricted food regimen and their weights were gradually reduced until they approximated 80% of the free-feeding weights, at which they were maintained for the duration of the study. Supplementary food needed to maintain this weight was given immediately after each session.

The rats were trained to press each of two levers under an FR 1 schedule of reinforcement, after which drug-discrimination training was initiated. During the training phase, the subjects were injected with either 10 mg/kg sodium pentobarbital or 0.9% saline solution (drug vehicle) and placed in the operant chamber. For the next 10 min the chamber was dark. Subsequently, the initiation of the session was signaled by illumination of the two houselights and, depending on the schedule in effect, the illumination of lights over each lever. For 3 of the subjects, responses on the right lever were reinforced after administration of 10 mg/kg sodium pentobarbital, and responses on the left lever had no programmed consequences. After administration of saline, responses on the left lever were reinforced for these subjects, and responses on the right lever had no programmed consequences. The reinforcement contingencies were reversed for the remaining 2 subjects.

At this time the schedule of reinforcement was changed from an FR 1 to a multiple FR FI schedule. The lights above the levers served as the discriminative stimulus for schedule components and were illuminated during the FI component but not during the FR component.

The values of the schedule were changed over a number of sessions until the terminal schedule values of FR 20 and FI 180 s were reached. There was a 10-s timeout after the completion of each schedule component, during which all lights were turned off and responses, if any occurred, were not recorded and had no scheduled consequences. A 90-s limited hold was also in effect, such that if the subjects did not earn the reinforcer within 90 s after it became available during the FI or did not complete the FR in 90 s, the timeout period occurred and the multiple schedule switched to the next component. The FR and FI components alternated after each reinforcer or expiration of the limited hold. The FR or FI schedule was presented as the initial component for each session on a single-alternation basis counterbalanced among the subjects. Pentobarbital or saline was given according to a counterbalanced double-single alternation series, which permitted each stimulus condition (drug or saline) to be paired with each initial schedule an equal number of times. Training sessions were 30 min in length and were conducted 6 days per week.

Behavior was considered stable when subjects completed the FR component with at least 80% of their responses on the correct lever and

the majority (over 50%) of the responses under the FI component on the correct lever, for a total of six consecutive sessions. Only the data for the initial schedule component (FR or FI) were used to determine stability because reinforcer delivery could function as a discriminative stimulus for lever selection in the subsequent schedule components (Schuster & Balster, 1977). The six consecutive sessions were composed of three sessions in which the FR was the initial component and three sessions in which the FI was the initial component. Pentobarbital or saline administration occurred equally often during these sessions.

Stimulus control (drug generalization) test sessions were conducted on Tuesdays and Fridays with control sessions conducted on Sundays, Mondays, Wednesdays, and Thursdays. The initial schedule component, FR or FI, continued to be presented on a single-alternation basis to ensure an equal number of control sessions under each initial schedule condition. Order of administration of pentobarbital or saline was counterbalanced, with 3 subjects exposed to one order and the remaining 2 subjects to the other, as outlined in Table 1. A test session was conducted only if the subject maintained the training criteria of 80% correct responding under the initial FR and a majority of correct responses under the initial FI for the preceding two control sessions (one saline, one pentobarbital). The FR and FI components were the initial components in test sessions equally often. Test sessions terminated after each schedule component had been presented once. During test sessions, responses on either lever were reinforced according to the schedule requirements. The 90-s limited hold and 10-s timeout also were in effect during test sessions.

To determine the pattern of stimulus control under the FI, responses were recorded in 10 bins of 18 s each. Responses on each lever after the FI had elapsed (i.e., reinforced responses during the limited hold) were also recorded in a separate time bin.

To determine whether the FI and FR schedule components differentially influenced the ability of the subjects to detect the drug stimulus, a signal-detection theory (SDT) analysis of the pentobarbital, PCP, and MK-801 dose–response data was performed. This method of analysis was developed by McCarthy and Davison (1980) for point estimates of discriminability (PED) and bias (PEB). To classify responses for the SDT analysis, the proportion of responses on the pentobarbital lever after each test dose (hits, H) and the proportion of responses on the saline lever (misses, M) were compared with the proportion of pentobarbital responses emitted under the preceding saline control session (false alarms, FA) as well as the proportion of saline lever responses (correct rejections, CR). Because of the multiplication of the values within the formula, when responding was 100% on the pentobarbital or saline lever, a value of 99% was used for calculation, and when the subjects did not respond at all on the pentobarbital or saline lever, a value of 1% was inserted into the formula for calculation purposes. The formula for the PED is $0.5 \log (H \times CR)/(FA \times M)$. The formula for the PEB is $0.5 \log (H \times FA)/(CR \times M)$. This SDT analysis has previously been applied to drug-discrimination data by McMillan and Wenger (1984).

Table 1

Order of control and test sessions.

Initial schedule component	Rats R199, R201, and R203	Rats R200 and R202
FR	Saline	Pentobarbital
FI	Pentobarbital	Saline
FR	Test	Test
FI	Pentobarbital	Pentobarbital
FR	Saline	Saline
FI	Test	Test
FR	Pentobarbital	Saline
FI	Saline	Pentobarbital
FR	Test	Test
FI	Saline	Saline
FR	Pentobarbital	Pentobarbital
FI	Test	Test

Dose–response determinations were conducted once for pentobarbital and once for each of the test drugs. Doses of the test drugs were administered in a between-subjects counterbalanced order. Dose–response curves were generated for sodium pentobarbital, *d*-amphetamine sulfate (both from Sigma Chemical Co.), phencyclidine (PCP) hydrochloride, and MK-801 maleate (both from the National Institute on Drug Abuse). All drugs were dissolved in physiological saline and administered intraperitoneally in a constant volume of 1

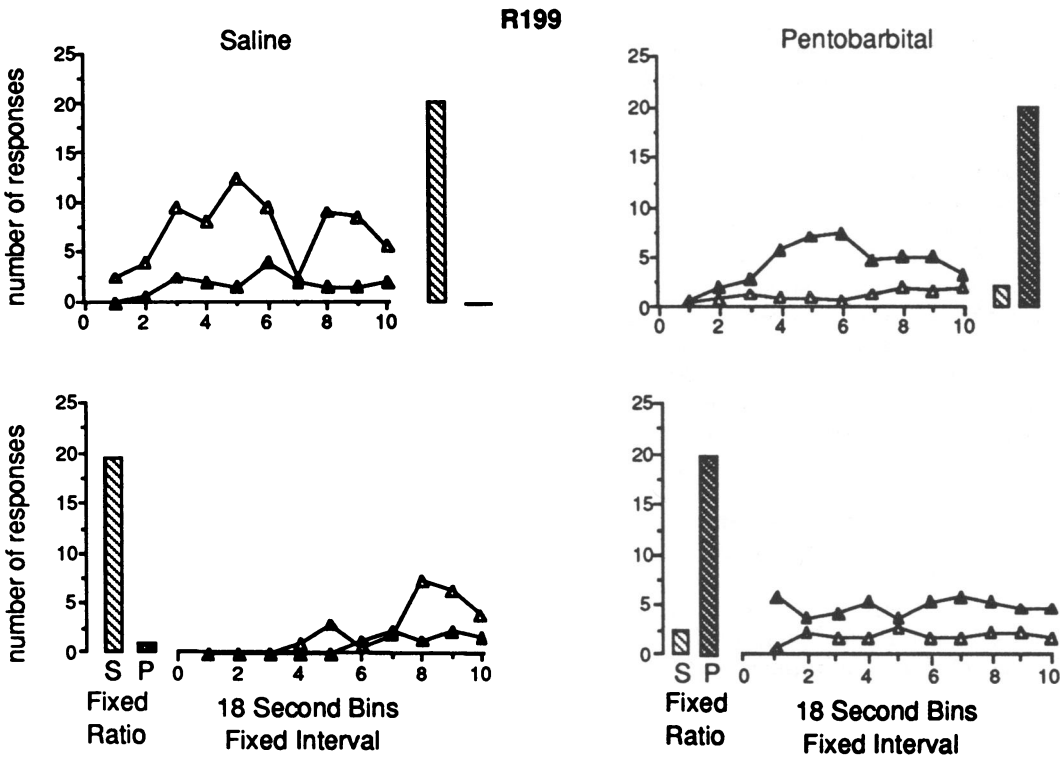

Fig. 1. Data from the saline (left panels) and pentobarbital (right panels) sessions immediately prior to the start of pentobarbital dose–response testing for Subject R199. The top panels show the FI as the initial schedule component of the session, and the bottom panels show the FR as the initial schedule component. Saline responses are represented as unfilled triangles for the FI component and as the lightly shaded bar for the FR component. The FI data are plotted as total number of responses made within each of 10 18-s bins.

mL/kg 10 min prior to session initiation. All drug doses are expressed as the salt.

RESULTS

Over the course of a session, subjects emitted the distinctive patterns of responding associated with each of the component schedules. During the FR component, responding occurred at a steady rate (0.58 responses per second after saline administration and 0.43 responses per second after pentobarbital administration, averaged across subjects). The group mean FI component response rate after saline was 0.31 responses per second, whereas after pentobarbital subjects averaged 0.28 responses per second. Over the entire session, response rate was low at the beginning of the FI and increased later in the interval. However, during the initial FI component of the session, rates of responding were relatively constant after the first few bins under both saline and pentobarbital conditions. This steady state of responding over much of the FI component is shown in Figure 1 for Rat R199 after saline and pentobarbital, both with the FI component occurring first and the FR component occurring first. Other animals generated similar patterns of FI responding.

Figure 1 also shows that Rat R199 responded on both the correct and incorrect levers across the FI component. This pattern of responding resulted in a relatively high number of incorrect responses under the FI compared to the FR component. Under the FR, particularly after the administration of saline, there were very few incorrect responses. Other rats also made more responses on the incorrect lever under the FI component than under the FR component. Differences in incorrect responses under the FI and FR components are also apparent in the control data of Figure 2.

Figure 2 shows each rat's mean percentage of responding on the pentobarbital lever for

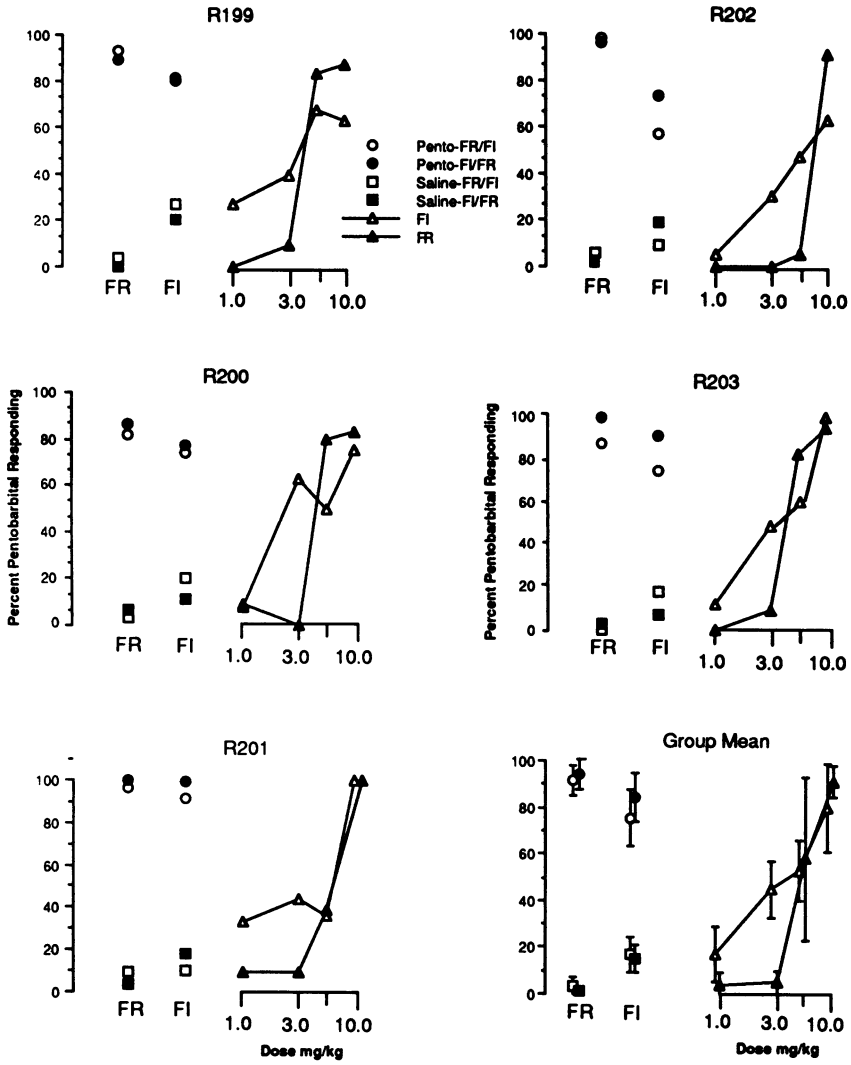

Fig. 2. Control and pentobarbital dose–response data for individual subjects and for the group mean. The unconnected symbols on the left side of the individual-subject graphs show average values when the FR (open symbols) or the FI (closed symbols) was the initial schedule component with saline (squares) or pentobarbital (circles) administered prior to session initiation. The right side of each individual-subject graphs shows the percentage of pentobarbital responding under the FI (open triangles) and the FR (closed triangles) components during the pentobarbital dose–response determination. The group mean is shown in the lower right panel. The vertical bars represent ± *SD* of the group means.

the training sessions as well as the individual pentobarbital dose–effect curves. Under control conditions, few errors occurred under the FR compared to the FI component. During the pentobarbital dose–response determination, at low doses (1.0 and 3.0 mg/kg), all rats made more responses on the pentobarbital lever under the FI component compared to the FR component. As the dose of pentobarbital was increased, the rats emitted an increasingly greater proportion of FI responses on the pentobarbital lever, which resulted in a graded dose–response curve. In contrast, the pentobarbital dose–effect curve under the FR component was steeper with, typically, an all-or-none pattern. Low doses produced few pentobarbital responses, whereas higher doses (5.6 to 10.0 mg/kg) produced a high percentage of pentobarbital responses. An exception is Rat R201, which emitted approximately 40% pen-

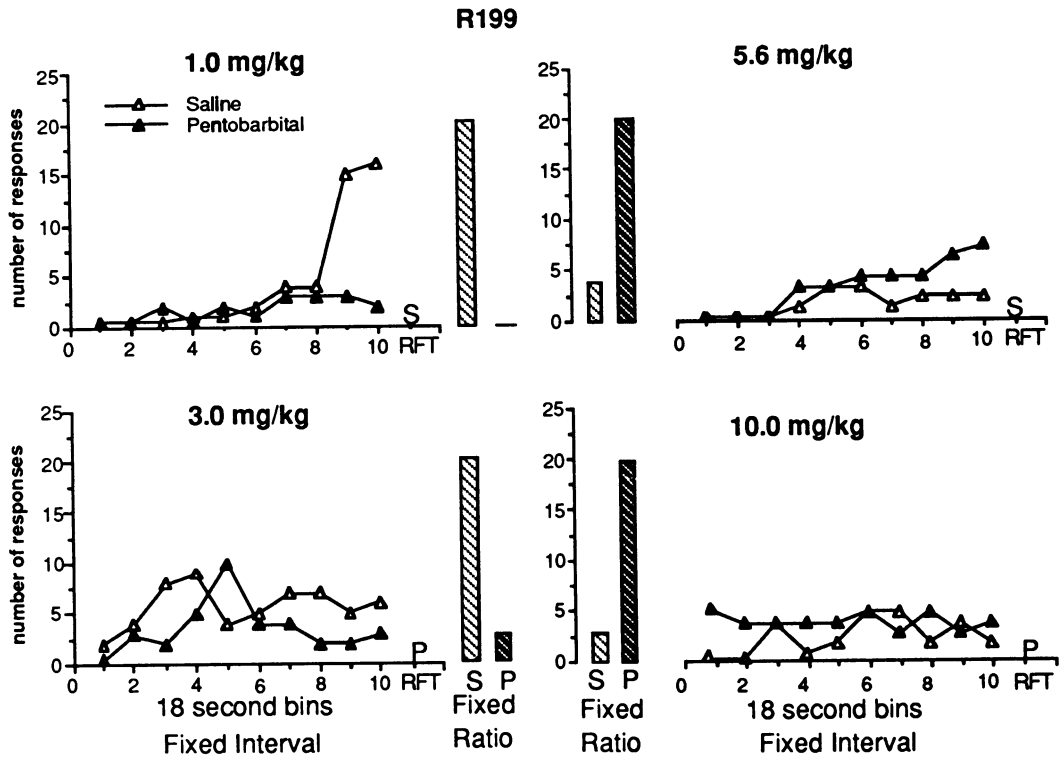

Fig. 3. Effects of the differing doses of pentobarbital on responding under the FI and FR components by Subject R199. The symbols and order of the schedule components are designated as in Figure 1. The letters located over the RFT bin indicate whether responding on the pentobarbital lever (P) or the saline lever (S) was reinforced during the dose–response test.

tobarbital-appropriate responding under the FR after 5.6 mg/kg pentobarbital. The graded dose–response curve of the FI component and the steeper dose–response curve of the FR component usually resulted in a crossing of the two curves.

Figure 2 also shows that the graded dose–effect curve for the FI component seen in the individual subjects is reflected by the mean FI curve. The mean dose–effect curve for the FR component is also graded, but this is largely an artifact of averaging, because a graded dose–effect curve was not observed in 4 of the 5 rats.

When responses were reinforced under the initial component, it was possible that responding under the second component could be controlled by the initial reinforcer acting as a discriminative stimulus (Schuster & Balster, 1977). However, if responding were controlled by the initial reinforcer, then incorrect responding under the second component should have been eliminated. From inspection of the control data of Figure 2, it can be seen that, with the exception of responding under the FR after saline administration, the rats continued to emit incorrect responses under the FR and FI components when they were presented second.

Figure 3 shows the effects of each dose of pentobarbital on the behavior of R199 during each of the test sessions. Again, the behavior of this rat is representative of the behavior of the others. As the dose of pentobarbital increased, so did the proportion of pentobarbital responses under the FI schedule component. Little pentobarbital responding occurred under the FR component until the higher doses (5.6 and 10.0 mg/kg) were reached, at which time most of the FR responding was completed on the pentobarbital lever. Also, as in the control sessions, behavior was determined by the schedule component and stimulus condition and not by the initial reinforcer. This lack of control by the initial reinforcer can be seen by examination of R199's behavior after 3.0 mg/kg pentobarbital. At this dose, the FI was the

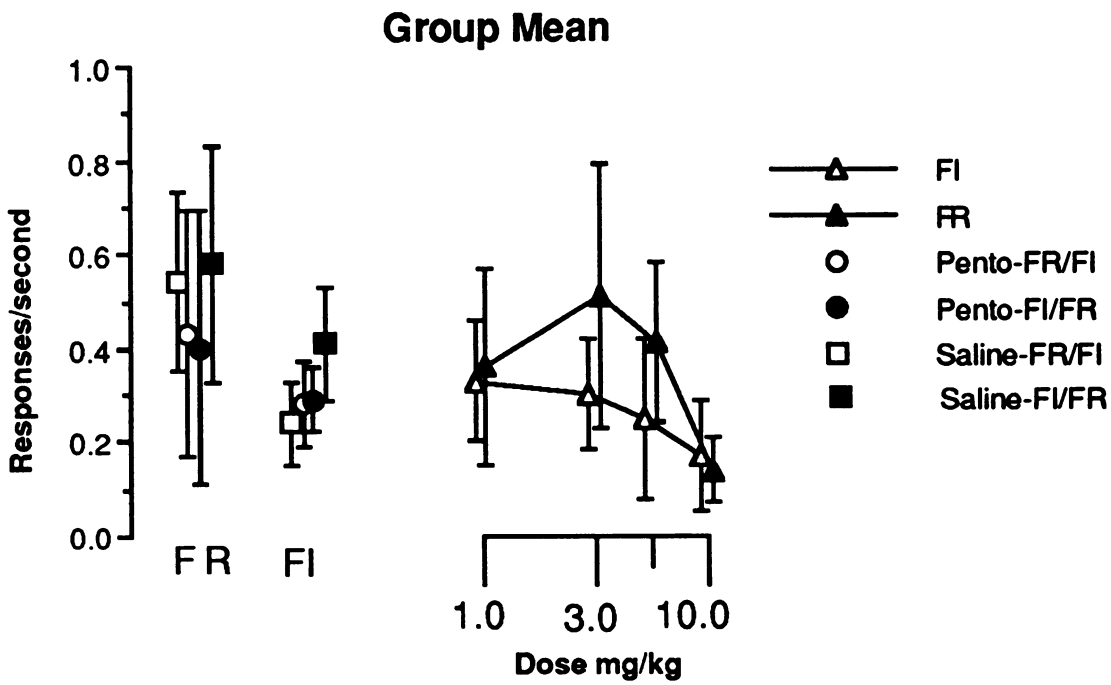

Fig. 4. Mean response rates under the FR and FI schedule components averaged across subjects for the control and pentobarbital dose–response test sessions. Details are as in Figure 2.

initial component and responding on the pentobarbital lever was reinforced, but during the subsequent FR component, responding on the saline lever was reinforced. Other examples of the dominance of stimulus control by the drug occurred for R199 at doses of 5.6 and 10.0 mg/kg pentobarbital. Although the FR was the initial component at these doses and responding was reinforced on the pentobarbital lever, R199 continued to respond on both the pentobarbital and saline levers under the FI component.

Figure 4 shows the effects of pentobarbital administration on mean response rate. Under training conditions, the rats generally had a higher mean rate under the FR than the FI, but variability was high. Pentobarbital tended to produce a downward trend in the rate of responding, but even after the dose of 10.0 mg/kg the response rates were only marginally reduced compared to the highly variable control rates. There were no clear differences between FI and FR components for effects of pentobarbital on rates of responding. After the dose of 17.8 mg/kg, none of the subjects responded.

Figure 5 shows a signal-detection theory (SDT) analysis of the pentobarbital dose–response data. Under both the FI and the FR components, as the dose of pentobarbital increased, there was an increase in the point estimate of discrimination (PED). However, under the FI component, the PED increased only slightly for 2 (R199 and 202) of the 5 rats across the doses of pentobarbital, whereas R201 and R203 showed a large increase in discriminability only at the dose of 10.0 mg/kg and R200 showed an intermediate increase at this dose. In comparison, under the FR component, 3 rats (R199, R200, and R201) showed a large increase in the PED from 3.0 to 5.6 mg/kg pentobarbital, and the PED of a 4th rat (R202) showed a large increase at 10.0 mg/kg. Only R203 showed a relatively equal gradation of PED values under the FR component.

The bottom panels of Figure 5 show a greater point estimate of bias (PEB) towards saline responding at low doses of pentobarbital under the FR component than under the FI component. As the dose of pentobarbital increased, there was a decrease in the bias under both components with bias decreasing at a greater rate under the FR component. After the high-

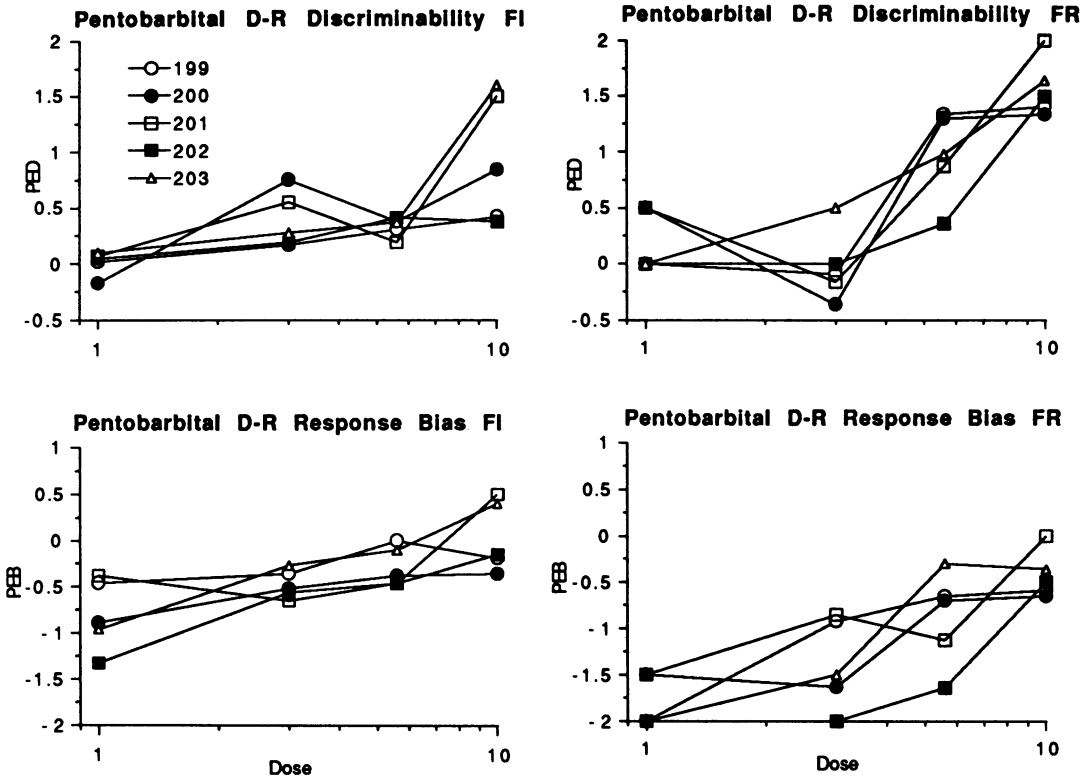

Fig. 5. Signal-detection theory analysis of the pentobarbital dose–response data for the FI (left panels) and the FR (right panels) schedule components. The point estimate of discriminability (PED) values (top panels) and the point estimate of bias (PEB) values (bottom panels) are shown for Subjects R199 (open circles), R200 (closed circles), R201 (open squares), R202 (closed squares), and R203 (open triangles).

est dose of pentobarbital, the differences in bias between schedule components had decreased, but the bias remained slightly greater towards the saline response under the FR component compared to the FI component.

The numbers of reinforcers earned by each rat under each schedule component and stimulus condition are shown in Table 2. These data are important in that, during a drug-discrimination procedure, if there is a disparity in the number of reinforcers earned under saline and drug conditions it may influence choice (Koek & Slangen, 1982). As an example, if rats earn more reinforcers under saline compared to the number earned under the drug condition, they may be biased towards responding on the saline lever (De Vry, Koek, & Slangen, 1984). Thus, the response bias (bottom panels of Figure 5) may be due to the difference in the number of reinforcers they earned while under saline or pentobarbital.

The data in Table 2 reveal that during the 56 control sessions the rats averaged approximately six FI and FR opportunities per session and earned 634 reinforcers, 58.5% of which were earned after saline. Comparing the number of reinforcers earned under the two components reveals that 50.5% were earned under the FI and, thus, 49.5% were earned under

Table 2

Number of reinforcers earned during 56 control sessions.

	FI first				FR first			
	Saline		Pento-barbital		Saline		Pento-barbital	
Rat	FI	FR	FI	FR	FI	FR	FI	FR
R199	16	21	20	11	15	24	12	19
R200	11	20	12	6	9	20	13	7
R201	18	18	16	12	19	19	9	6
R202	24	21	20	14	21	19	16	9
R203	15	23	21	11	14	24	19	10
Total	84	103	89	54	78	106	69	51

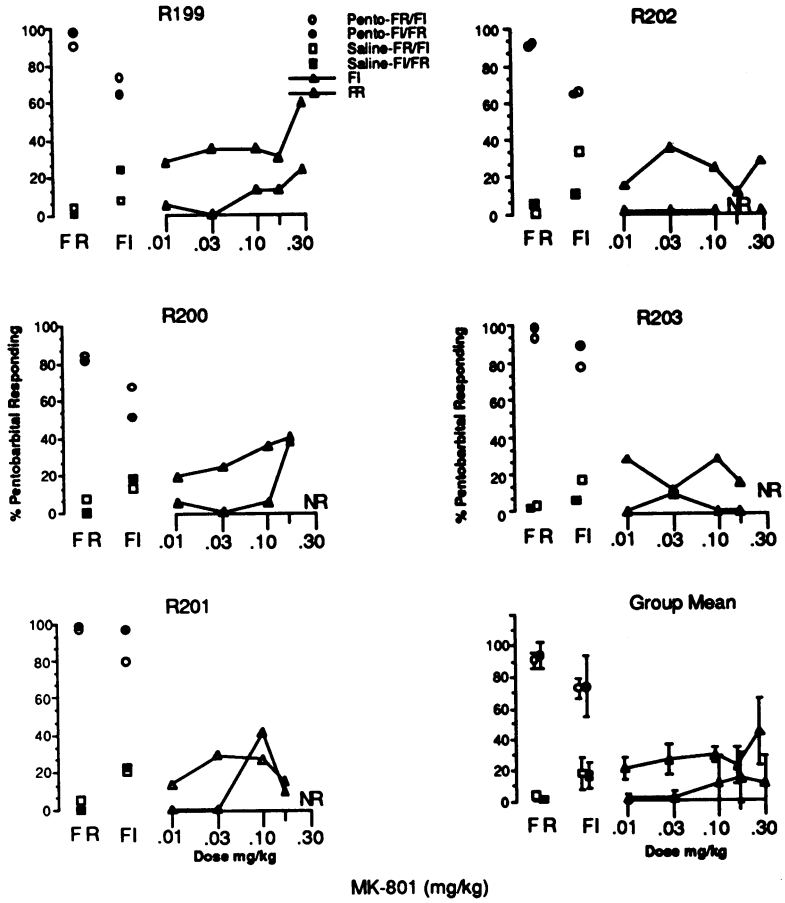

Fig. 6. Control and MK-801 dose–response data for individual subjects and the group mean. "NR" means the subject did not respond at that dose under the specified schedule component. Other details are as in Figure 2.

the FR component. When saline was administered prior to the session, a higher percentage of reinforcers were earned under the FR component compared to the number of reinforcers earned under the FI component (32.9% to 25.6%). After pentobarbital administration, the rats earned more reinforcers under the FI than under the FR component (24.9% to 16.6%). From Table 2, it can also be seen that whether the FR or FI was the initial component made little difference in the number of reinforcers earned.

Figure 6 shows the dose–response data for the administration of MK-801. Responding did not generalize completely to MK-801 in any rat. However, increased pentobarbital responding did occur under both the FI and FR components for Rats R199 and R200 after MK-801, and Rat R201 produced an above-baseline level of pentobarbital responding under the FR component for the dose of 0.1 mg/kg MK-801. Rats R202 and R203 showed little tendency for the pentobarbital stimulus to generalize to MK-801 under either schedule component. The mean dose–response curve also provided little evidence for stimulus generalization between pentobarbital and MK-801.

Figure 7 shows the results of the SDT analysis of the MK-801 dose–response data. Under the FI schedule component, increasing dose of MK-801 had little effect on either discriminability or response bias. Under the FR component, Subjects R199, R200, and R201 showed small increases in discriminability as the dose of MK-801 increased. Response bias under the FR component showed only small and inconsistent changes after administration of MK-801. However, bias was greater to-

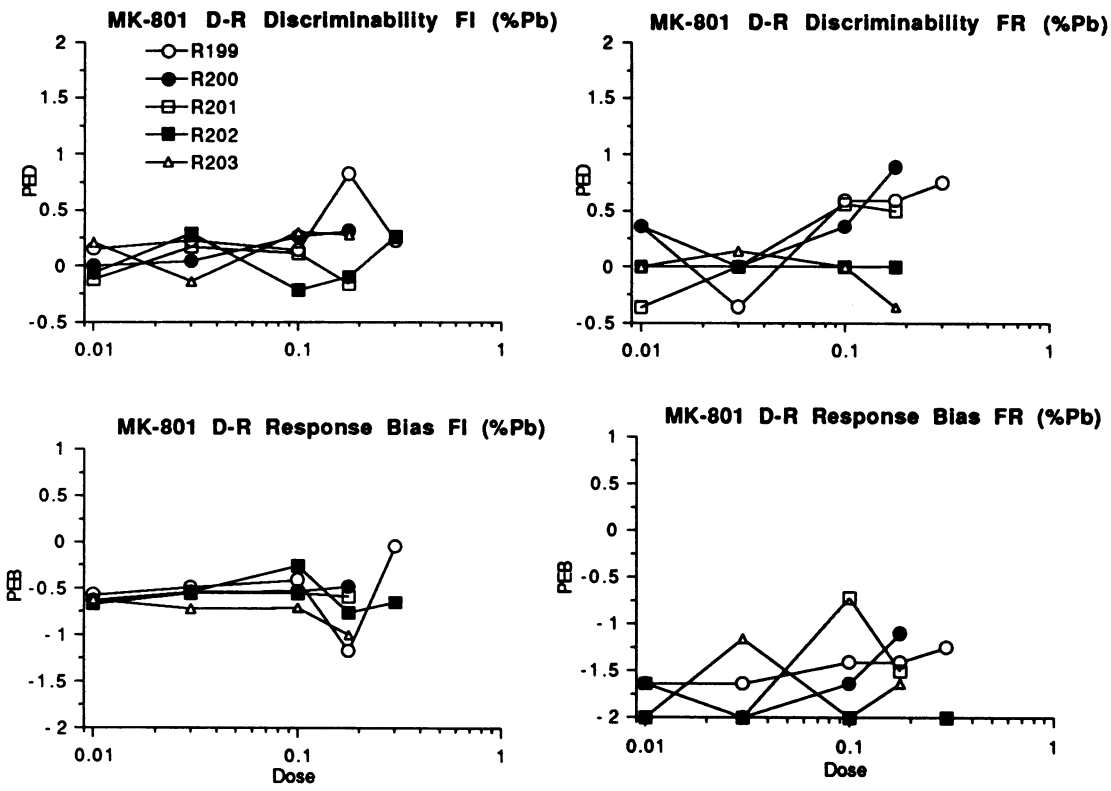

Fig. 7. Signal-detection theory analysis of the MK-801 dose–response data. Details are as in Figure 5.

wards the saline response under the FR component compared to the FI, although this difference was not affected by dose of MK-801.

The dose–response determinations for PCP are shown in Figure 8. For all rats, there was some increase in responding on the pentobarbital lever after PCP. Rats R199 and R200 both emitted a relatively high proportion of pentobarbital responding under the FR component after 1.7 mg/kg PCP, with R200 showing almost complete generalization at this dose. Both subjects responded on both levers under the FI component, with R199 making the highest proportion of pentobarbital responses after 1.0 mg/kg PCP and then gradually decreasing the proportion of pentobarbital responding at higher doses. Rat R203 responded almost entirely on the pentobarbital lever under the FI component after 3.0 mg/kg PCP. Rats R201 and R202 also showed increased pentobarbital lever responding under the FI component after at least one of the higher doses of PCP.

The mean PCP dose–effect curve (Figure 8), like the individual subject curves, shows responding occurring on both levers under the FI. All 5 rats failed to complete the FR requirement of 20 responses after 3.0 mg/kg PCP, and some rats failed to complete the FR requirement after other doses. These results were not due to an inability to press the lever, because these rats typically emitted more than 20 responses under the FI component during the same sessions. When the rats did not complete the FR component, their data were excluded from the dose–response graphs.

Figure 9 shows the results of the SDT analysis of the PCP dose–response data. For the most part, the FI component data are similar to those of MK-801 in that there is little effect of dose of PCP on discriminability or response bias. Under the FR component, the PED data reveal some variability, particularly at the dose of 1.7 mg/kg. The PEB data, however, show that for each of the 4 subjects that responded, the degree of the PEB remained steady until

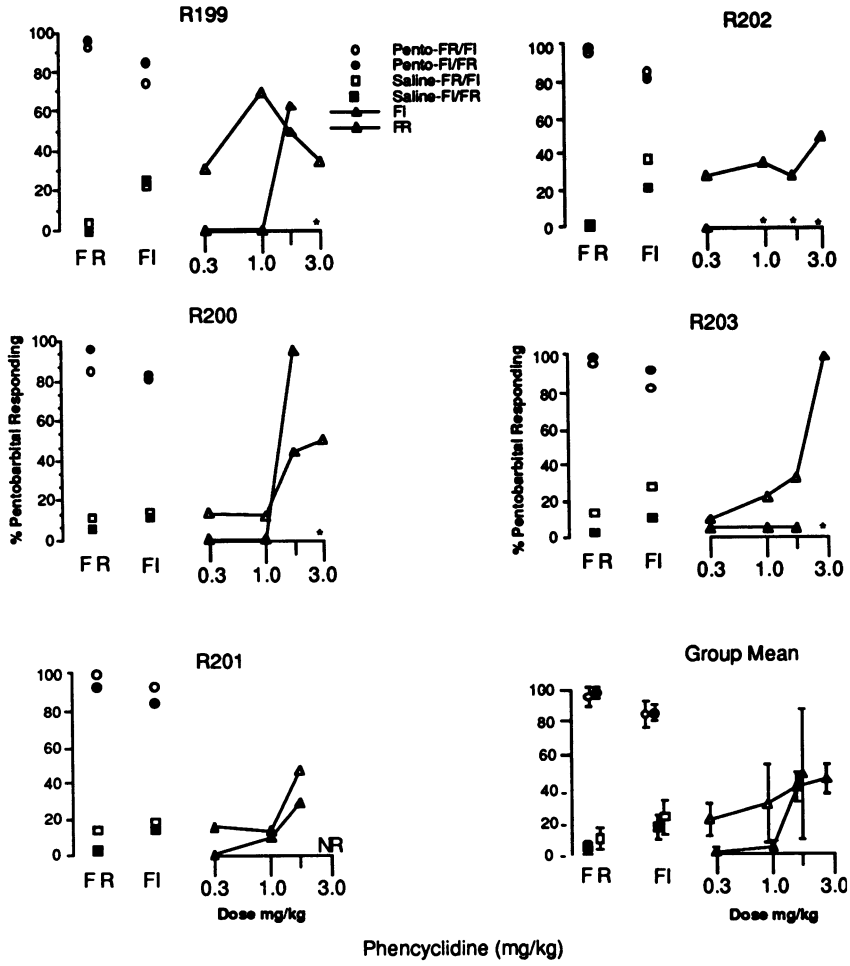

Fig. 8. Control and PCP dose–response data for individual subjects and the group mean. "NR" means the subject did not respond at that dose under the specified schedule component. * indicates that the subject failed to complete the FR 20 requirement at that dose of PCP. Other details are as in Figure 2.

the dose of 1.7 mg/kg. At this dose, there was a decrease in the amount of bias towards the saline response.

Figure 10 shows the dose–response curve for *d*-amphetamine. Although the rats occasionally responded slightly above baseline levels on the pentobarbital lever, pentobarbital responding was weak after *d*-amphetamine, and the mean curve shows little evidence for generalization of pentobarbital to *d*-amphetamine under either schedule. Because there was no evidence of stimulus generalization from pentobarbital to *d*-amphetamine, an SDT analysis of the *d*-amphetamine data was not conducted.

DISCUSSION

In rats trained to discriminate pentobarbital from saline under a mult FI FR schedule, the shape of the pentobarbital dose–response curve depended on the schedule component. The pentobarbital dose–response curve for the FI component was graded, whereas the dose–response curve for the FR component was steeper with a comparatively abrupt shift from responding on the saline key to responding on the pentobarbital key with increasing dose. Another difference between schedule components was the relatively large number of errors made under the FI compared to the FR com-

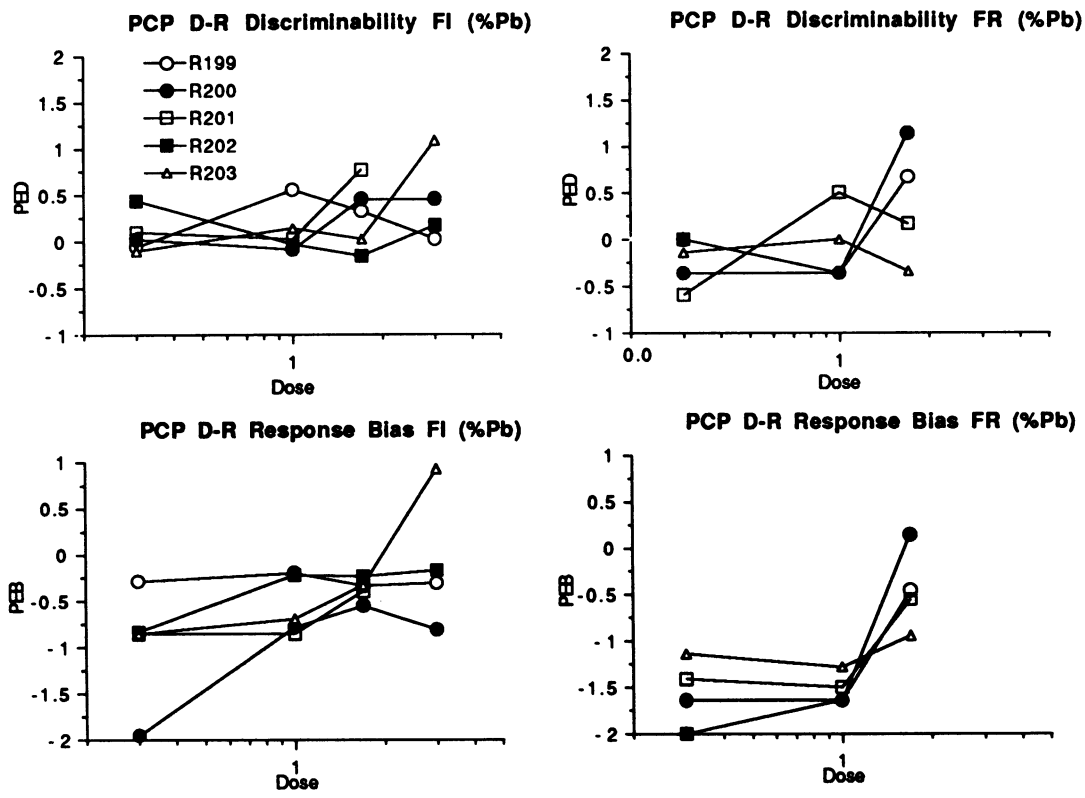

Fig. 9. Signal-detection theory analysis of the PCP dose-response data. Details are as in Figure 5.

ponent during control sessions. Thus, the schedule of reinforcement determined both the degree of stimulus control by the training dose of pentobarbital and the shape of the pentobarbital dose–response curve.

Discriminability (PED) increased and response bias (PEB) decreased with increasing doses of pentobarbital. Therefore, it is difficult to determine the extent to which the dose-related change in behavior was a function of either PED or PEB. This result is unusual in that a primary advantage of a SDT analysis is its ability to separate the influence of sensory changes from changes produced by nonsensory factors such as differential reinforcement contingencies (Appel & Dykstra, 1977; Baird & Noma, 1978; Blough & Blough, 1977; Galanter, 1984; Nevin, 1981; Wright, 1974). Thus, typically, it is possible to determine how sensory factors affect choice by holding the reinforcement contingencies constant while the discriminability of the stimulus is altered. However, in the present study, all pentobarbital responses during the test sessions were designated as "hits" and, therefore, all saline responses were designated as "misses." At low doses of pentobarbital, the subjects responded primarily on the saline lever and, thus, mostly misses were recorded, with a low PED and a high negative PEB as the result. As the dose of pentobarbital increased there was an increase in the number of hits and, accordingly, an increase in the PED and a decrease in the PEB. Thus, this designation of responses as hits and misses produced a dependency between the PED and the PEB.

An increase in the PED is usually interpreted as an increase in the ability to discriminate the presence and absence of the pentobarbital stimulus. However, particularly under the FR schedule, the subjects were discriminating the presence of the pentobarbital stimulus from its absence at the low doses (1.0 mg/kg for the FI component and, typically, up to 3.0 mg/kg for the FR component), as can be seen from the dose–response curves of Figure 2. Thus, in this case, the PED is not so much an indicator of discriminability as it is an in-

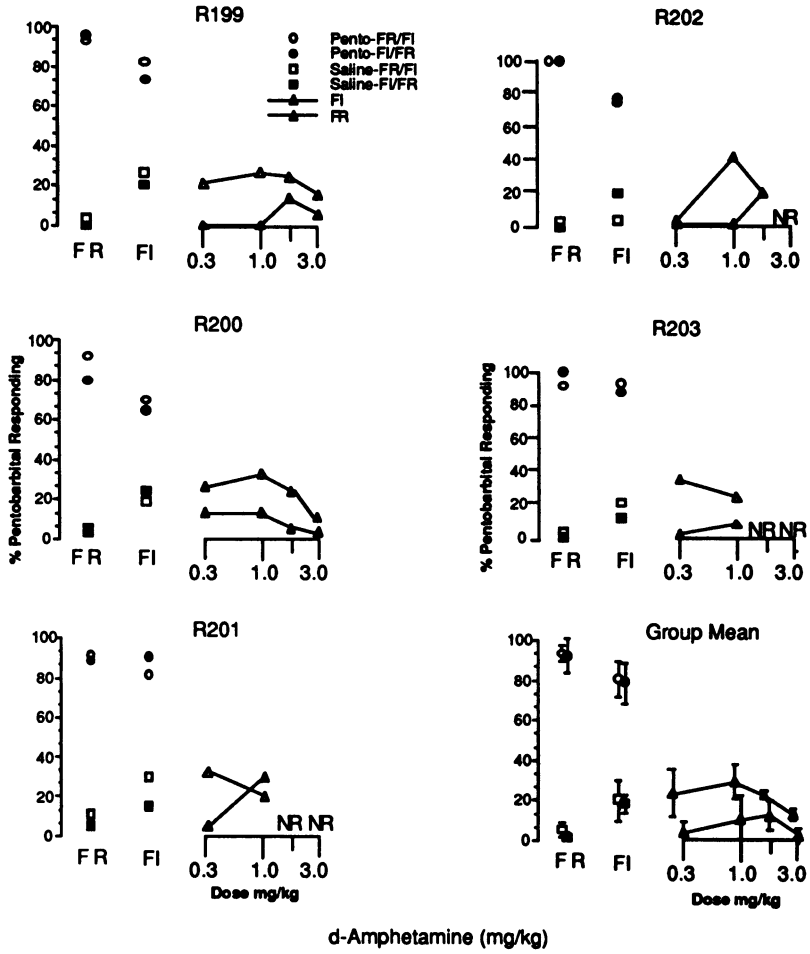

Fig. 10. Control and *d*-amphetamine dose–response data for individual subjects and the group mean. "NR" means the subject did not respond at that dose under the specified schedule component. Other details are as in Figure 2.

dicator of the detectability of the pentobarbital stimulus.

According to the formula, the PEB is a measure of the ratio of pentobarbital responses to saline responses during test and saline control sessions. Thus, with responding restricted primarily to the saline lever during test sessions with low pentobarbital doses, and responding also restricted primarily to the saline lever during the saline control sessions, bias towards the saline response is high. As the dose of pentobarbital increases, there is an increase in pentobarbital responding during the test sessions and a decrease in bias towards the saline response. Thus, because of the manner in which hits and misses are designated, both the PED and PEB change as the dose of pentobarbital changes. This simultaneous change in both the PED and the PEB with changes in the dose of a training or test drug has been reported previously by McMillan and Wenger (1984).

Although the simultaneous changes in the PED and PEB within the schedule components makes it difficult to determine their independent influence upon behavior, this problem does not arise when considering differences in the PED and PEB between schedule components. Under the FR component, the PED showed a larger increase with increasing dose than under the FI component. This suggests that the subjects were better able to detect the presence of the pentobarbital stimulus under the FR than under the FI component. The rats were also more biased towards saline responding under the FR component than under the FI component at all doses of pentobarbital.

As Koek and Slangen (1982) have noted, if the subjects in a drug-discrimination procedure receive a greater proportion of the total reinforcers under one of the stimulus conditions, then they may show a response bias towards that stimulus condition. In the present study, the rats received more reinforcers during training under the FR component after saline administration than after pentobarbital administration (Table 2). Thus, the disparity in the number of reinforcers earned may explain why the rats showed a higher degree of bias towards the saline response under the FR component. However, it does not explain the slight bias towards the saline response observed under the FI component. Under the FI component, responses were reinforced about equally after pentobarbital and saline (Table 2). Thus, some other factor(s) must contribute to the bias toward responding on the saline key.

Willetts and Balster (1989), in a study investigating the stimulus effects of pentobarbital and N-methyl-d-aspartate (NMDA) antagonists, reported that the rats in their study responded at an average of 37.3% of total responses on the pentobarbital lever after the maximally effective dose of MK-801. These authors concluded that although the discriminative stimulus effects of MK-801 and pentobarbital did not fully overlap, there was some degree of stimulus similarity between the two drugs and, thus, partial generalization. The present study confirms this finding. Partial generalization of the stimulus effects of MK-801 to those of pentobarbital occurred for some subjects under both schedule components.

PCP produced variable amounts of responding on the pentobarbital lever. Varying degrees of generalization of the pentobarbital stimulus to that of PCP have been reported (Massey & McMillan, 1987; McMillan & Wenger, 1983; Willetts & Balster, 1989). In the present study, the responding of Rat R200 suggested complete generalization between the PCP stimulus and that of pentobarbital under the FR component, whereas Rat R199 responded predominantly on the pentobarbital lever under this schedule component. Under the FI component, all 5 subjects produced above-baseline pentobarbital responding at some doses, whereas the responding of Rat R203 showed complete generalization. There was a suggestion that the FR dose–response curves were quantal and the FI curves graded, but the data are limited and no firm conclusions can be made about the role of the schedule of reinforcement and generalization of the pentobarbital stimulus to PCP.

It has been assumed that the reinforcer in a drug-discrimination procedure acts as a discriminative stimulus to control subsequent responding (Schuster & Balster, 1977). Thus, only responses prior to the first reinforcer delivery are typically used as a measure of stimulus control. The present study showed that the first reinforcer did not control lever selection in the subsequent schedule component. Responding was clearly under the control of the presence or absence of the pentobarbital stimulus, regardless of the response previously reinforced. Mathis and Emmett-Oglesby (1989) have reported that if, in a drug-discrimination procedure, a rat is administered either cocaine or pentylenetetrazole and the session is immediately begun, most rats will receive reinforcement initially on the saline lever and will continue to respond on this lever even when the drug stimulus comes into effect later in the session. However, these authors also concluded that if a subject has little experience with reinforcement on the saline lever prior to the initiation of the drug stimulus effect, then the drug stimulus will control behavior and not reinforcement for responding on the saline lever. Because the rats in the present study were limited to one reinforcement exposure, these results cannot be generalized to repeated reinforcement of a response. However, they do support the conclusion of Mathis and Emmett-Oglesby (1989) that if a rat has little experience with reinforcement under one stimulus condition, this reinforcement experience will not interfere with its subsequent responding.

An important question in all studies of stimulus generalization is whether stimulus generalization gradients are continuous or quantal (Bickel & Etzel, 1985). A quantal gradient suggests that the stimulus functions as a unitary phenomenon that is either present or absent, and that continuous generalization gradients are an artifact of averaging responses to the two states over time. A continuous gradient suggests that the stimulus effects of the test drug gradually become more discriminable as the dose of the test drug is increased. Mathis and Emmett-Oglesby (1990) and Colpaert (1986, 1987) suggested that the detection of the drug stimulus is an all-or-none event

(quantal) and that continuous gradients result from the averaging of data from subjects with differing absolute thresholds for detection of the drug stimulus. However, the present results suggest that whether a quantal or continuous gradient is obtained depends not so much upon the stimulus, but, rather, is dependent upon the schedule of reinforcement maintaining responding. It was found that the FR schedule usually produced a quantal gradient that, if averaged across subjects, can produce a graded dose–response curve, whereas the FI schedule produced a continuous gradient in the individual animals.

A possible explanation for the differing effects of the FI and FR schedule components comes from operant experiments investigating choice behavior. In a typical choice study, two manipulanda are made available to the subject and responses on each of the manipulanda are reinforced according to specific, independent, schedules of reinforcement (de Villiers, 1977). The relative distribution of responses across the two schedule alternatives indicates the relative value of the alternatives as discriminated by the subject (Herrnstein, 1970). In choice situations, it has been shown that subjects will match their relative rate of responding to the relative rate of reinforcement, or value, that is received from the two schedules (Herrnstein, 1970). In other words, the behavior of subjects in choice situations conforms to that predicted by the generalized matching law (Baum, 1974), and, as such, the differential responding is a reflection of the subject's preference for one, compared to the other, schedule alternative.

During typical training under a drug-discrimination procedure, the subject is faced with a choice of two manipulanda; responding on the manipulandum associated with the stimulus condition in effect is reinforced, whereas responding on the other manipulandum usually has no programmed consequences, or is "inconsequential" (Colpaert, 1987, p. 343). However, responding on this manipulandum does in fact have a scheduled consequence. This responding undergoes the process of extinction during the differential reinforcement of correct responding. Thus, during training, and later during control sessions, the subject has a choice between two schedules; that is, the subject is exposed to a concurrent-schedule choice situation in which responses are reinforced under one schedule but are extinguished under the other schedule. In addition to manipulanda position or key color indicating the differential reinforcement contingencies as in the typical concurrent-schedule choice situation, in drug discrimination it is also the presence or absence of the training drug stimulus that serves this function. Thus, the presence or absence of the drug stimulus, through association with reinforcement, serves to indicate the differential reinforcement contingencies between the two schedule choices.

It is possible that what determines the shape of the dose–response function is not whether the discriminative stimulus is quantal or continuous. Rather, the shape of the dose–response function may be determined by preference for the concurrent schedule that provides the highest rate of reinforcement. In concurrent FR FR schedules, in which the subject discriminates the reinforcement densities of the two schedules, it will typically restrict its responding to the one schedule that provides the highest rate of reinforcement (or the lowest ratio requirement). Thus, a quantal choice relationship results (Davison & McCarthy, 1988; Herrnstein & Loveland, 1975). According to this analysis, subjects responding under FR drug-discrimination test or training sessions emit responses so as to maximize the number of reinforcers earned. In other words, with the drug-discrimination procedure typically employing a concurrent FR extinction schedule, during training and testing the subject will choose the schedule with the highest probability of reinforcement, as indicated by the degree of presence of the drug stimulus, and will respond on this schedule in a quantal manner.

Matching under a concurrent FI FI schedule occurs through the distribution of responses across the two alternatives in time (Davison & McCarthy, 1988; White & Davison, 1973). Subjects match relative response rate to relative reinforcement rate by switching responding from one schedule to the other. Unlike the FR schedule, reinforcement is not dependent on the number of responses, but, rather, is dependent on the time of responding. Thus, subjects can gain a greater number of reinforcers by distributing their responses to match the ratio of reinforcers delivered under the two FI schedules rather than by restricting their responding to only one schedule. If one FI schedule delivers a greater number of reinforcers than the other, then a greater amount

of responding will be spent on that one, rather than the other, FI schedule.

In drug discrimination with an FI schedule, the subjects are again placed in a choice situation. Because reinforcement during training is restricted to one manipulandum, responding should be restricted to this manipulandum if it is a clear choice. However, reinforcement has been obtained for responding on both manipulanda during training, and if the presence and absence of the drug stimuli are not perfectly discriminable, then there is some probability that reinforcement will be obtained from the manipulandum associated with the stimulus that is not in effect. Thus, mixed responding during training and during testing may be a reflection of the subjects matching their relative rate of responding to the relative probability of reinforcement from the two alternatives. As the drug dose is varied, the probability of reinforcement being available across the two choices also varies. To match this change in the probability of reinforcement, subjects alter their relative rate of responding across the two manipulanda. Therefore, according to a matching law analysis, the relative rate of responding should match the relative rate of reinforcement obtained under the two choices, as indicated by the degree of presence of the drug stimuli. This matching of relative response rate and relative probability of reinforcement would produce a graded dose–response curve.

This matching law analysis does not provide support for either the continuous or quantal position regarding stimulus generalization gradients. It may be that as the dose of the drug increases, the degree of stimulus control of behavior changes in a continuous manner, and it is this continuous change that caused the graded dose–response curve seen under the FI schedule component. However, as Colpaert (1987) has noted, subjects in a drug-discrimination procedure are trained to respond only in the presence or absence of a specific dose of a training drug. Thus, it may be that the drug stimulus operates in a quantal manner and what the subjects are responding to is the probability that the training drug stimulus is present. The difference between the two interpretations is that in the former, responding is controlled by the similarity of the test drug stimulus to the training drug stimulus, whereas in the latter, responding is controlled to the degree to which subjects detect the training drug state.

The results of this study have shown that the schedule of reinforcement determines, to a large extent, the distribution of responses in a two-lever pentobarbital discrimination. Although this interpretation is not novel (Holloway & Gauvin, 1989), it does emphasize the point that schedules of reinforcement are powerful determinants of drug-discrimination behavior. The results also point to the possibility of an integration of the field of concurrent-choice schedules with the field of drug discrimination.

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